1653

Attorney Docket No. 172.2US.DC2
**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**



In re application of: Bischofberger et al.

Serial No.: 09/801,164 Group No.: 1653

Filed: March 7, 2001 Examiner: D.Lukton

For: NUCLEOTIDE ANALOGS

**Assistant Commissioner for Patents**

**Washington, D.C. 20231**

# AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

**STATUS**

2. Applicant is

☐ a small entity - verified statement:

☐ attached.

☐ already filed.

☒ other than a small entity.

---

**CERTIFICATE OF MAILING (37 CFR 1.8 (a))**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Robin Torres
(Type or ~~print~~ name of person mailing paper)

Date: March 20, 2003

Robin Torres
(Signature of person mailing paper)

## EXTENSION OF TERM

3. The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply

(a) [X] Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17 (a)-(d)) for the total number of months checked below:

| | Extension (months) | Fee for other than small entity | Fee for small entity |
|---|---|---|---|
| [ ] | one month | $110.00 | $55.00 |
| [ ] | two months | $410.00 | $205.00 |
| [X] | three months | $930.00 | $465.00 |
| [ ] | four months | $1,450.00 | $725.00 |

Fee $ 930.00

**If an additional extension of time is required please consider this a petition therefor.**

[ ] An extension for _____ months has already been secured and the fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ _____

**OR**

(b) [ ] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

## FEE FOR CLAIMS

4. The fee for claims (37 CFR 1.16(b)-(d)) has been calculated as shown below:

| | (Col. 1) | | (Col. 2) | (Col. 3) | SMALL ENTITY | | | OTHER THAN A SMALL ENTITY | |
|---|---|---|---|---|---|---|---|---|---|
| | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NO. PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE | ADDIT. FEE | *OR* | RATE | ADDIT. FEE |
| TOTAL * | 1 | MINUS ** | 20 | = 0 | X 9 = | $ | | X18= | $ |
| INDEP. * | 1 | MINUS ** | 3 | = 0 | X42= | $ | | X84= | $ |
| ☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM | | | | | +140= | $ | | +280= | $ |
| | | | | | TOTAL ADDIT. FEE | $ | *OR* | TOTAL ADDIT. FEE | $ |

(c) ☒ No additional fee for claims is required.

**OR**

(d) ☐ Total additional fee for claims required $ _____

## FEE PAYMENT

5. ☐ Attached is a check in the sum of $ _____

☒ Charge Account No. 07-1250 the sum of $ 930.00

A duplicate of this request is attached.

## FEE DEFICIENCY

6. Authorization to Charge Additional Fees

☒ The Commissioner is hereby authorized by this document to charge any additional fees which may be required by this paper and during the entire pendency of this application to Account No. 07-1250 , except the issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311 (b).

Reg. No. 27,043

Tel. No.: (650 ) 522-5878

**SIGNATURE OF ATTORNEY**

Max D. Hensley

Type or print name of attorney

Gilead Sciences, Inc.

333 Lakeside Drive

P.O. Address

Foster City, CA 94404

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Robin Torres
(Type or print name of person mailing paper)

Date: March 20, 2003

Robin Torres
**(Signature of person mailing paper)**

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re PATENT APPLICATION of | ) | Group Art Unit: 1653 |
| | ) | Attorney Docket No. 172.2US.DC2 |
| Bischofberger et al. | ) | Examiner: D. Lukton |
| | ) | |
| Serial No: 09/801,164 | ) | |
| | ) | |
| Filed: March 7, 2001 | ) | |
| | ) | |
| Title: NUCLEOTIDE ANALOGS | ) | |



## AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is responsive to the Patent and Trademark Office action mailed September 20, 2002. A Request for a Three Month Extension of Time is submitted herewith, whereby the date for response is March 20, 2003.

Claim 52 remains the sole claim in this case.

Amended claim 52 as shown in the attached mark-up. A clean copy of claim 52 is also attached.

Claim 52 was rejected under 35 U.S.C. 112 first paragraph as not being based on an enabling disclosure. The examiner relies upon a number of citations for the

proposition that prodrugs cannot be predicted to be active *a priori* based solely on structure.

Shabat discloses prodrugs of etoposide which are activated *in vivo* by a catalytic antibody. Shabat's express intention was to prepare a prodrug that was *only* activated by the antibody, and not by any endogenous enzymes ("...we attempted to improve this strategy with the design of prodrugs of etoposide that are activated by a tandem retro-aldol/retro-Michael reaction *not known to be catalyzed in nature.*" right column, page 7528, emphasis added). Shabat does not stand for the proposition advanced by the examiner because Shabat specifically designed the prodrugs to *not* be activated *in vivo*.

Smal also does not support the examiner's position. Smal teaches that all of the prodrugs produced in fact were hydrolyzed in vivo. The fact that some were hydrolyzed more rapidly than others (i.e., the leucyl derivative) is simply a matter of choice and of degree, not a showing that undue experimentation was required to find a suitable prodrug. On the contrary, only *one* out of the 5 prodrugs made was found to be "unsuitable." This can hardly be said to be an exemplar of undue experimentation.

The examiner relies on Saboulard for the proposition that "prodrugs of AZT are not effective". This would appear to be an overstatement. Saboulard states that the AZTMP triesters failed to "afford *pronounced* antiviral activity in CEM/TK- cells" (p. 701). In addition, this observation only applied to one of the two test systems (CEM/TK- cells; page 697). Table 1 shows a range of activity, but at least half the compounds tested had activity in the vicinity of the superior L-alanine derivatives. Again, this is far from evidence of "undue experimentation".

Jaffar et al. are cited for their disclosure of allegedly ineffective prodrugs in Table 1. Inspection of Table 1 shows three ineffective compounds and three effective ones. It can hardly be said that the Jaffar et al. disclosure places any cloud over

prodrugs. Half of the Jaffar et al. compounds worked. It would not have required undue experimentation in these circumstances to obtain an active compound.

Miyauchi et al. teach that prodrugs of cephalosporins are generally successful when esterified at the C-4 carboxyl group (references 4-10), but that in the instance of the unique cepahlosporin Miyauchi was concerned about this approach would not be useful. Instead, Miyauchi attempted converting the parental drug to include an unusual ring-opened structure, together with esterification of the carboxyl group. Metabolic conversion of the analogue prevented significant recovery of the parent. As such, this work then is an exception to the general rule that cephalosporin esters are effective prodrugs and does not indict the concept of ester prodrugs in this class of therapeutics.

The examiner notes that Hadad et al. failed to find biological activity with 4 out of 5 ester prodrugs. It would not be undue experimentation to have to screen 5 compounds to find an active one. "Undue" experimentation does not mean certainty, or even that considerable work would not be required. Routine screening of a few compounds is not undue experimentation. In any case, Hadad reports that a number of previous VPA amide prodrugs were successful, and these efforts must be taken together with Hadad's work to obtain a complete picture of the prodrug success rate with VPA. By no stretch will the cited literature support the view that obtaining VPA prodrugs constitutes a particularly difficult experimental obstacle, much less "undue" experimentation.

The examiner appears to have misinterpreted Langer et al. The examiner states that attaching a peptide to daunorubicin or doxorubicin "eliminated" activity. The Langer NPY-Dauno-HYD compound (see Fig. 1 for structure – this is a peptide conjugate) was effective in fact (lines 6-9 in the 3rd paragraph of column 1, page 1344). The lack of activity to which the examiner refers is the lack of activity of this compound in cells not bearing the NPY receptor. However, this was an advantage because it

would produce "selective tumor targeting" (same paragraph, last 9 lines). Two other peptide conjugates were inactive, but once again the pattern of the examiner's citations is holding up – the need to screen only a few prodrug analogues to find one that would work.

Mamber et al. is quite similar to the preceding citations in that it shows a substantial percentage of candidate prodrugs being active, i.e., in Mamber et al. half the phosphate prodrugs were effective (BMS180661 and BMS180820). Again, this can hardly be said to be an exemplar of undue experimentation.

Remarkably, Niemi et al. also obtained a 50% success rate. The 3 pivaloyloxymethyl ester compounds were active, whereas the 3 benzoyloxypropyl esters were not.

The examiner apparently equates unpredictability with undue experimentation. Unpredictability is merely one part of the multifaceted *Forman* test for undue experimentation. As the cases have pointed out, the fact that experimentation is permitted under Section 112 means that absolute predictability is not required. If absolute predictability was required, then it would not be necessary to do any experimentation at all. Some experimentation is acceptable under the statute. The question is whether it is "undue."

The examiner correctly refers to the *Forman* test but then ignores it all except for the unpredictability aspect. The examiner is requested to provide a complete *Forman* analysis.

It might be helpful to the examiner to consider a case that actually looked at the quantitative aspect of undue experimentation. A copy is attached of *In re Wands* 8USPQ2d1400, 1403 (Fed. Cir. 1988), an appeal from a PTO rejection urging that undue experimentation was required to select a successful monoclonal antibody. In this case,

four instances (fusions) were successful, while five were not. This is similar to the success rates seen in the references relied upon by the examiner as illustrative of undue experimentation. The citations relied upon by the examiner do not conform with the requirements of law and therefore are not a measure of undue experimentation. In the absence of a complete *Forman* analysis and supporting citations, the rejection cannot be sustained. The examiner is requested to reconsider and withdraw the rejection under 35 U.S.C. 112 first paragraph.

Claim 52 also was rejected under 35 U.S.C. 112 second paragraph as being indefinite for the recitation $N(R^{6A})$, the examiner pointing out that $N(R^{6A})_2$ is what is intended. This is correct, and claim 52 has been so amended.

Applicants have not received an examiner-initialed copy of the PTO-1449 form filed with applicants' disclosure statement filed December 7, 2001 (copy attached). Applicants would be grateful for this document in due course.

This application is now believed to be in condition for allowance.

Respectfully,

Max D. Hensley, Reg. 27,043
*Phone: (650) 522-5878*
*Fax: (650) 522-5575*
*email: max_hensley@gilead.com*

Attachments: *In re Wands*
Disclosure Statement Form 1449